REMARKS

Claims 50 to 76 are pending in this application.

The Rejections under 35 U.S.C. §112

Claim 63 is rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite. In particular the Office Action states that the term "substantially" in claim 63 is indefinite. Claim 63 recites in the last line ". . . wherein the analgesic composition is substantially free of opioid antagonist." This rejection is respectfully traversed. The term "substantially" is a commonly used term in claims. A search of the U.S. Patent and Trademark Office on line database for the use of the phrase "substantially free of" uncovered over 20,900 patents. A few representative examples are presented.

In U.S. Patent No. 5,069,898, claim 4 recites as follows (emphasis added herein):

> 4. The composition of claim 1 wherein said cosmetically acceptable carrier is **substantially free of** lower alkyl alcohol.

In U.S. Patent No. 5,747,042, claim 8 recites as follows:

> 8. The method of claim 4 wherein said exhaust gas contains less than 10 percent volume of oxygen, is **substantially free of** ethylene.

In U.S. Patent No. 6,689,399 claim 1 recites as follows:

> 1. A composition, comprising:
> (a) a capsaicinoid;
> (b) a primary amine selected from the group consisting of glucosamine, galactosamine, and pharmaceutically acceptable salts thereof, said primary amine being present at a concentration of between about 18% and about 25% by weight, and
> (c) a pharmaceutically effective carrier, said carrier being effective to promote transdermal movement of at least one component of said composition

upon contacting the skin of a patient with said composition; said composition further being **substantially free of** herbs or herbal preparations.

The specification at page 7 lines 1-5 clearly indicates the meaning of "substantially free of". In particular, the specification states that the opioid antagonists are ". . . substantially excluded from the analgesic composition since they pose a risk for precipitating opioid withdrawal when taken by a chronic opioid abnser." Accordingly, one skilled in the art would realize that the recitation "substantially free of opioid antagonist" refers to a composition having no amount of opioid antagonist which would precipitate opioid withdrawal in a chronic opioid abuser. There is no lack of clarity. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

The Rejections under Prior Art

Claims 63-66 are rejected under 35 U.S.C. §103(a) as being obvious over Caruso et al. in view of U.S. Patent No. 4,574,080 ("Roswall et al."). Caruso et al discloses a composition comprising the NMDA receptor antagonist dextromethorphan in combination with morphine in a 1:1 ratio. Roswall et al. is cited for disclosing pharmaceutical compositions containing active agents in which one is present in an extended release form. It is respectfully submitted that one skilled in the art would not find it obvious to combine those references. Moreover, Applicant has provided evidence of unexpected results illustrating the superiority of the claimed composition.

It is not at all obvious that better results can be obtained by releasing the dextromethorphan immediately as opposed to having both the opioid and the dextromethorphan as extended release agents. Caruso et al. teaches that dextromethorphan as NMDA receptor

antagonist enhances the analgesic properties of morphine. But neither Caruso et al. or Roswall et al. disclose or suggest that loading NMDA receptors with dextromethorphan soon after drug administration and then metering out the opioid analgesic may pharmacologically increase the enhancing effects of the NMDA receptor antagonist on the analgesic drug such that less dextromethorphan is required to provide the necessary ratio of dextromethorphan to analgesic. This reduces any adverse side affects of dextromethorphan.

Referring now to Applicant's specification page 11, line 9 to page 12, line 16, it is explained that a 1:1 ratio of morphine to dextromethorphan enhances analgesic effect of morphine. Further increases in the relative amount of detromethorphan, for example to a 1:2 ratio, increases the enhancement even further but may increase the risks of adverse side effects of dextromethorphan. A higher ratio of dextromethorphan to opioid analgesic may be obtained systemically with lower amounts of dextromethorphan, if 100% of the dextromethorphan is immediately released while a portion of the opioid analgesic is released over time. The release of 100% dextromethorphan as an immediate release component (IR) provides greater amounts of dextromethorphan to morphine in an extended release component (ER) on an absolute μmolar basis at the systemic level, compared to where both drugs are administered as extended release components (ER-ER) as shown in Table 1 (page 12 of the specification).

As is apparent from Table 1, there is a 2-fold or more increase in absolute ratio of analgesic to dextromethorphan at the systemic level when equimolar amounts of dextromethorphan IR are administered compared with dextromethorphan ER. Thus, 50% less dextromethorphan IR will achieve, in this example, a minimum 1:1 ratio of dextromethorphan to the analgesic at the systemic level. The lower amount of dextromethorphan required to provide

the needed ratio of dextromethorphan to analgesic will minimize or reduce any adverse side effects attributed to dextromethorphan when the analgesic composition of the present invention is administered to a patient.

These surprising results are neither disclosed nor suggested by either of the cited references whether taken individually or in combination and rebuts any inference of obviousness. Therefore, the combination of an extended release opioid analgesic as listed in claim 63 with an immediate release dextromethorphan is submitted to be allowable subject matter.

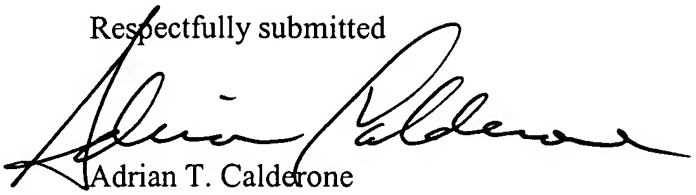
Further distinguishing claim 63 over the cited prior art is the recitation that the analgesic composition is substantially free of opioid antagonist, which is neither disclosed nor suggested by either cited reference.

Accordingly it is respectfully submitted that claim 63 and all claims depending therefrom are submitted to be allowable over the cited prior art. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

For at least the reasons stated above all of the pending claims are submitted to be in condition for allowance, the same being respectfully requested.

Respectfully submitted



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